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ON THE PERIPHERAL VASCULAR
SYSTEM

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

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By
ALMA FOGELBERG

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SOME EFFECTS OF BULBOCAPNINE ON THE PERIPHERAL VASCULAR SYSTEM

ALMA FOGELBERG

Bulbocapnine is one of the alkaloids derived from *Corydalis cava*. Structurally it bears a resemblance to apomorphine (1). Although some of its pharmacological effects are similar to those of related alkaloids, Peters (2) and others more recently have shown that it produces quite specific physiological disturbances.

The bulk of the experimental work with bulbocapnine has been stimulated by its ability to produce, in mammals, a syndrome known as bulbocapnine catatonia. De Jong (3, 4, 5), Schaltenbrand (6, 7, 8, 9, 10, 11, 12), Kok (13) and Henry (14, 15) have all demonstrated experimentally the peculiar involvement of the central nervous system in bulbocapnine catatonia. Autonomic disturbances are also known to occur. Mode (16) and Peters (2) were among the first to note changes in heart's action, respiration, salivation, lachrimation and blood pressure.

Since 1933, Leese and his associates have been working with several aspects of the peripheral action of bulbocapnine. Roberts and Leese (17) and Leese and Roberts (18) found that, in cats, the steady state which could be produced in nerve-muscle preparations *in situ* decreased after bulbocapnine was injected. The steady state usually disappeared altogether when large enough doses of bulbocapnine were given. During bulbocapnine intoxication, there was little or no tendency for the tension level developed by the muscle preparation to follow changes in the systemic blood pressure. Muscular fatigue was more readily produced under the influence of bulbocapnine. The usual increases and decreases in muscle tension resulting from graded

doses of adrenaline intravenously did not appear following the injection of bulboCAPnine. Fogelberg and Leese (19) indicated their belief that, under bulboCAPnine, peripheral vascular changes are responsible for the development of fatigue in continuously stimulated nerve-muscle preparations *in situ*. Histological preparations from the animals showed a great increase in the vascularity of the skin and muscle. It was felt that venous pressure determinations would aid in deciphering the nature of the peripheral vascular disturbances. In a series of 6 cats and 2 dogs, prepared for the simultaneous recording of muscle tension and arterial and venous blood pressures, it was found that intravenous doses of bulboCAPnine amounting to less than 1 mgm. per kilogram caused, in general, small increases in venous pressure and small decreases in arterial pressure. There was sufficient inconsistency to indicate that a special series of animals should be used to record arterial and venous pressure changes under the influence of varying doses of bulboCAPnine.

EXPERIMENTAL

A series of 11 dogs were used in this study. The experiments were done under ether, without an auxiliary anesthetic. Previous to the intraperitoneal injection of bulboCAPnine, control doses of adrenaline, mecholyl, pitressin and histamine were given intravenously. Following the maximal arterial and venous pressure changes induced by the bulboCAPnine, the same doses of the above drugs were repeated. The intraperitoneal doses of bulboCAPnine, based on the weight of the animal, varied from 3 to 60 mgm. per kilogram.

The arterial pressure was recorded by means of a mercury manometer, connected directly with the left carotid artery. The venous pressure was recorded by means of a water manometer connected with the right jugular vein. In 2 cases the venous cannula was the "T" tube type, and in the others a washout cannula and mixing bulb were placed so as to record from the peripheral end of the vein. The left femoral vein was cannulated for injection purposes.

As soon as the arterial and venous blood pressures had es-

tablished fairly stable levels, assay doses of the drugs to be used were determined. The testing agents and their standard strengths were as follows: Adrenaline (Parke Davis) 1:100,000; pitressin (β -hypophamine, Parke Davis) 1 unit per cubic centimeter; acetyl-beta-methyl-choline chloride (mecholy¹, Merck) 1:2,000,000; histamine acid phosphate (Lilly) 1:25,000. These standards were suitable to give the desired rise or fall of blood pressure in doses of 0.5 cc. or less. If the volume of the assay dose exceeded 1 cc. the strength of the standard was raised. In addition to the standards listed above, bulbocapnine¹ (Merck) 1:1,000 was assayed in several of the experiments. When the assay was complete, bulbocapnine was given as a total intraperitoneal dose in some of the experiments, whereas, in others, it was divided, part of the dose being given intraperitoneally and part intravenously. The literature indicates that this procedure is satisfactory if time for action is allowed. The doses of bulbocapnine given on the basis of body weight of the animals were taken directly from 1 cc. sterile ampules containing 100 mgm. of bulbocapnine in 1 cc.

The time allowed between assay doses before and after bulbocapnine varied according to the time required for the blood pressure to again establish a stable level. Upon occasion, doses of the drug larger than the assay amount were used. Each dose was washed into the femoral vein with 5 cc. of Ringer's solution. Frequent controls of Ringer's solution were injected to check the injecting system.

RESULTS

A total of 644 measurements of arterial and venous pressure curves were made on 11 animals (see table 1).

The administration of the intraperitoneal dose of bulbocapnine depressed both arterial and venous blood pressures within ten to thirty minutes in every experiment. During the period before the injection of bulbocapnine, the arterial and venous pressures showed corresponding pressure changes in 4 of the 11

¹ The bulbocapnine and mecholy¹ used in these studies were furnished through the kindness of the Merck Laboratories.

animals. After the injection of bulbo-capnine, the venous pressure level appeared to be more dependent upon the arterial pressure, since a direct relationship between the two appeared in 9 of the 11 animals.

The primary fall in arterial and venous pressures which took place during the first half hour after the intraperitoneal injection of bulbo-capnine was not correlated with the dose. Results showed that the 17 mgm. per kilogram dose produced the smallest decrease in arterial pressure, and the 48 mgm. per kilogram dose produced the smallest decrease in venous pressure. The 16 mgm. per kilogram dose produced the greatest fall in arterial

TABLE 1

Distribution of 644 blood pressure changes produced by adrenaline, pitressin, mecholyl and histamine before and after the injection of bulbo-capnine in eleven dogs

TESTING AGENTS	ARTERIAL PRESSURE		VENOUS PRESSURE	
	Before bulbo-capnine	After bulbo-capnine	Before bulbo-capnine	After bulbo-capnine
Adrenaline.....	76	66	75	58
Pitressin.....	27	27	27	27
Mecholyl.....	40	45	40	40
Histamine.....	20	28	20	28

pressure, and the dose of 60 mgm. per kilogram produced the greatest fall in venous pressure.

The average fall in arterial pressure for all the experiments following the intraperitoneal injection of bulbo-capnine amounted to 37 mm. Hg, or 37 per cent of the average arterial pressure at the time of the injection. The corresponding fall in venous pressure amounted to 28 mm. H₂O or 50 per cent of the average venous pressure at the time of the injection (see tables 2 and 3).

The arterial pressure gradually increased in all but two of the experiments following the initial drop produced by the bulbo-capnine. In each of these 2 cases the pressure fell below 55 mm. Hg which is near a critical shock level.

Before the injection of bulbo-capnine, the venous pressure

TABLE 2
Average fall in arterial blood pressure one-half hour after the injection
of bulbocapnine

BULBOCAPNINE DOSE	ARTERIAL PRESSURE		
	At time of injection	One-half hour after injection	Per cent decrease
<i>mgm. per kgm.</i>	<i>mm. Hg</i>	<i>mm. Hg</i>	<i>mm. Hg</i>
3	30	38	37
13	120	90	25
16	60	24	60
17	90	69	23
20	129	66	49
24	86	64	26
40	138	100	28
44	132	60	55
48	98	66	33
53	102	55	46
60	80	57	29
Average fall.....			37

TABLE 3
Average fall in venous blood pressure one-half hour after the injection of bulbocapnine

BULBOCAPNINE DOSE	VENOUS PRESSURE		
	At time of injection	One-half hour after injection	Per cent decrease
<i>mgm. per kgm.</i>	<i>mm. H₂O</i>	<i>mm. H₂O</i>	<i>mm. H₂O</i>
3	28	25	11
13	85	45	47
16	104	80	23
17	80	68	15
20	58	50	14
24	50	8	84
40	35	4	89
44	66	-11	117
48	65	60	8
53	22	-15	17
60	27	-6	122
Average fall.....			50

registered between 40 and 110 mm. H₂O, with the exception of one experiment in which it dropped to -10 mm. H₂O. After the injection of bulbo-*capn*ine the venous pressure fell to a negative level in seven of the eleven experiments. In two of the experiments the venous pressure fell to -20 mm. H₂O after the bulbo-

TABLE 4

*Average of percentage changes in arterial blood pressure in bulbo-*capn*inized dogs under ether anesthesia as produced by adrenaline, pitressin, mecholyl and histamine*

BULBOCAPNINE	ADRENALINE		PITRESSIN		MECHOLYL		HISTAMINE	
	Before bulbo- <i>capn</i> ine	After bulbo- <i>capn</i> ine	Before bulbo- <i>capn</i> ine	After bulbo- <i>capn</i> ine	Before bulbo- <i>capn</i> ine	After bulbo- <i>capn</i> ine	Before bulbo- <i>capn</i> ine	After bulbo- <i>capn</i> ine
<i>mgm. per kgm.</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
3	16	20	15		-35	-24		
13	40	10	47	121		-6	-60	-64
16	26	6	30	94	-19	-19	-76	-53
17			17		-90	-67		
20	11	4	12	26	-33	-34	-19	-26
24	27	8	15	40	-46	-17	-15	-13
40	11	7	10	52	-10	-7	-18	-18
44	15	8	9	24	-6	-11	-14	-18
48	15	8	11	13	-9	2	-12	-21
53	7	4	14	23	-9	-6	-12	-7
60	19	7	15	20	-12	-10	-12	-7
Average per cent change.....	19	8	18	46	-27	-18	-24	-23

The percentage increase or decrease in arterial blood pressure during each individual experiment is calculated on the basis of the recorded base line, i.e., a change of 10 per cent on a recorded base line of 100 mm. indicates an actual change of 10 mm., and a -10 per cent indicates a drop in pressure of 10 mm. Each figure in the above table represents the average percentage response to similar doses of the standard given before and after bulbo-*capn*ine.

*capn*ine was injected. As the effect of the drug wore off, the pressure gradually returned to levels above zero.

In comparing the average percentage changes in arterial pressure (table 4), it was found that bulbo-*capn*ine decreased the effectiveness of adrenaline 60 per cent and that of mecholyl 33 per cent. The effectiveness of pitressin was raised 250 per cent, whereas that of histamine remained unchanged.

The venous pressure was found to be much less responsive than arterial pressure, which is in accord with the findings of others (20). The same was generally true after giving bulbo-capnine except that the tendency for the venous pressure changes to follow arterial pressure changes was more in evidence.

TABLE 5

Average of percentage changes in venous blood pressure in bulbo-capnized dogs under ether anesthesia as produced by adrenaline, pitressin, mecholyl and histamine

BULBOCAPNINE	ADRENALINE		PITRESSIN		MECHOLYL		HISTAMINE	
	Before bulbo-capnine	After bulbo-capnine	Before bulbo-capnine	After bulbo-capnine	Before bulbo-capnine	After bulbo-capnine	Before bulbo-capnine	After bulbo-capnine
<i>mgm. per kgm.</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
3	-49		7		3			
13	6	2	75	-3		4	-60	-29
16	27	3	9	55	2	-3	29	1
17			12		71	23		
20	12	27	8	70	43	38	2	-159
24	0	5	-35	-53	5	9	3	9
40	1	-12	4	28	8	5	2	17
44	5	94	13	75	-4	52	-2	120
53	2	0	7	4	30	6	99	5
60	37	-23	7	18	6	34	11	28
Average per cent change.....	5	14	15	22	16	18	11	27

The percentage increase or decrease in venous blood pressure during each individual experiment is calculated on the basis of the recorded base line, i.e., a change of 10 per cent on a recorded base line of 100 mm. indicates an actual change of 10 mm., and a -10 per cent indicates a drop in pressure of 10 mm. Each figure in the above table represents the average percentage response to similar doses of the standard given before and after the bulbo-capnine.

In comparing the average percentage changes in venous pressure (table 5), it was found that bulbo-capnine increased the effectiveness of adrenaline three times, that of pitressin one and one-half times, and that of histamine two and one-half times. The effectiveness of mecholyl in raising venous pressure was unchanged by the bulbo-capnine.

DISCUSSION

An average fall in arterial pressure of 37 per cent accompanied by an average fall in venous pressure of 50 per cent after the injection of bulbo-*capnine* indicate that bulbo-*capnine* increases the size of the peripheral vascular bed. The results obtained with small intravenous assay doses of bulbo-*capnine* support this opinion because the vascular response resembles the response to histamine. Hechst (21) reported the overfilling of the pial capillaries following bulbo-*capnine* injection. Histological studies on the skin and muscle of decerebrate frogs and cats indicate that bulbo-*capnine* produces a peripheral vascular congestion (22). Bulbo-*capnine* in doses of 200 to 250 mgm. per kilogram in the rabbit produces distinct hyperemia of the ears (repeated observations on many animals) (23). A number of investigators have reported a static pulse following bulbo-*capnine* injection. It is suggested that a decreased excitability of the vasomotor mechanism may account for this observation. This would also explain the greater correlation between general arterial and venous pressure changes after bulbo-*capnine* injection than before.

In this series, the absence of progressive vascular effect with increased doses of bulbo-*capnine* may be partially explained on the basis of individual variation in susceptibility. These results are similar to those of Amadon and Craige (24).

It is suggested that bulbo-*capnine* depresses the vasomotor nerve endings of the peripheral vascular system, since adrenaline is only two-fifths as effective and mecholyl only two-thirds as effective after the injection of bulbo-*capnine* as before. On the other hand, pitressin and histamine, which are said to act directly on the smooth muscle are equally or more effective after bulbo-*capnine* than before.

The fall of 50 per cent in venous pressure occurring after the injection of bulbo-*capnine* indicates that the efficiency of the heart was not decreased in the dosage range of 3 to 60 mgm. of bulbo-*capnine* per kilogram of body weight. The fact that in 7 of the 11 experiments the venous pressure fell below zero after the injection of bulbo-*capnine* emphasizes the retained efficiency

of the heart in removing blood from the venous side of the circulation. There is no evidence from the records of venous pressure changes produced by bulbocapnine which indicates that cardiac decompensation is concerned in the syndrome of bulbocapnine catatonia.

SUMMARY

1. Arterial and venous blood pressures were recorded on eleven dogs under ether anesthesia and 644 pressure curves were measured before and after the intraperitoneal injection of bulbocapnine.

2. Assay doses of adrenaline, mecholyl, pitressin and histamine were injected intravenously to determine any change in their vascular effectiveness in the presence of bulbocapnine.

3. Doses of bulbocapnine ranging from 3 to 60 mgm. per kilogram produced an average decrease of 37 per cent in the arterial and 50 per cent in the venous blood pressure within 30 minutes after the injection.

4. It is believed that bulbocapnine interferes with the peripheral vasomotor mechanism because adrenaline and mecholyl are less effective in altering arterial pressure after bulbocapnine than before, whereas the effectiveness of pitressin and histamine is increased or unchanged.

5. These venous pressure studies tend to exclude cardiac decompensation as a factor in the vascular picture of bulbocapnine catatonia.

6. Venous pressure tends to have a higher correlation with arterial pressure after the injection of bulbocapnine than before. This may be due to a decreased irritability of the peripheral vasomotor mechanism.

7. It is suggested that the static pulse of bulbocapnine catatonia is due to a decreased irritability of the vasomotor mechanism.

8. It seems probable that the peripheral vascular changes precede the muscular phenomena of bulbocapnine catatonia and that the vascular change is concomitant with the bulbocapnine narcosis.

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